Raised Cerebrospinal Fluid Norepinephrine in Some Patients with Primary Hypertension

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SUMMARY To test whether central neurogenic factors participate in blood pressure elevation in primary hypertension, we studied the concentrations of: norepinephrine, epinephrine and dopamine-beta-hydroxylase (DBH) in cerebrospinal fluid (CSF); and norepinephrine, epinephrine, DBH and plasma renin activity (PRA) in plasma of 22 subjects (seven with primary hypertension, 11 normotensive patients with non-systemic neurological disorders, and four with secondary hypertension). Plasma and CSF norepinephrine (NE) were increased in primary hypertensives compared to normotensives. Cerebrospinal fluid norepinephrine was related to diastolic blood pressure, and systolic blood pressure when normotensive and primary hypertensives were taken together. The CSF norepinephrine of primary hypertensive patients was correlated with natural log PRA. The CSF norepinephrine was correlated inversely with age in primary hypertensive patients but not in the normotensive subjects. The low CSF norepinephrine and epinephrine, despite markedly increased plasma NE and epinephrine, in two patients with pheochromocytoma, indicate a blood-brain barrier for these neurohormones. The observations support the view that the central sympathetic nervous system is involved in the pathogenesis of primary hypertension, particularly in younger patients. (Hypertension 1: 255-260, 1979)

KEY WORDS • neurogenic mechanisms • primary hypertension • cerebrospinal fluid • norepinephrine

PLASMA norepinephrine concentrations are increased in an appreciable number of patients with primary hypertension. Hyperactivity of the central sympathetic nervous system might raise plasma norepinephrine and lead to the development of hypertension. Because of an efficient blood-brain barrier to norepinephrine (NE) it seems possible to evaluate central nervous system NE release by measuring NE in cerebrospinal fluid (CSF). Therefore, in this study, we compared CSF NE concentrations from patients with primary hypertension with those from normotensive patients with various neurological disorders. We found increased NE in CSF and plasma from the hypertensive group, which suggests that central sympathetic hypertonicity is associated with raised peripheral sympathetic nerve tone and elevated blood pressure in younger patients with primary hypertension.

Patients and Methods

The protocol was approved by the Research Committees of the Los Angeles County-University of Southern California Medical Center and at the White Memorial Medical Center. Written informed consents were obtained for the study.

Patients with Hypertension

We studied three men and four women with primary hypertension, averaging 40 ± 13 years of age (mean ± sd) (table 1). In four patients neurological examination including lumbar puncture resulted in the final diagnosis of tension headache. One patient with a minor paresis of the left leg 3 weeks before admission had a normal neurological examination at the time of lumbar puncture, another had seizures and a third was examined for a syncopal episode. None of the patients manifested cardiac hypertrophy by ECG and chest roentgenograms. Fundoscopic examination revealed K.-W. Grade I to II retinopathy. In addition to the seven primary hypertensive patients we also studied one man with renovascular hypertension verified by I.V. pyelography, renal angiography and renal vein renins, another man with Guillain-Barré-Syndrome and hypertension, and two women with surgically verified pheochromocytoma.
Patients with Normal Blood Pressure

Six men and five women with normal blood pressures with various neurological disorders were examined as control patients (table 1). Their mean age of 36 ± 11 years did not differ significantly from that of the patients with primary hypertension (p < 0.3). Syncopal episodes or seizures occurred 1 week to 6 months before puncture. One woman had repeated lumbar punctures for pseudotumor cerebri. Her CSF pressure was normal at the time of this study. Four of the normotensive patients with seizures were being treated with phenytoin at the time of study, and their mean values were calculated separately from the other normotensive subjects.

Protocol

Diuretics were discontinued 1 week and other antihypertensive drugs 2 weeks before examination. Patients were characterized as hypertensive if the average of the supine diastolic blood pressures measured on 3 different days prior to the study was equal to or higher than 90 mm Hg. Each subject was given a diet containing approximately 100 mEq of sodium per day for 2 days before the study. Urine was collected for determination of Na+ and creatinine for the 24 hours preceeding the study. All subjects fasted overnight. Blood samples via indwelling needle and blood pressures via aneroid sphygmomanometer were taken in the morning of the study after 60 minutes standing and again after 60 minutes supine. The average of three pressures taken 1 minute apart was used in each position. Lumbar puncture was performed with the patient in the left lateral position immediately after the supine blood samples and blood pressure measurements were made between 9:00 a.m. and 10:00 a.m.

The second 6 ml of CSF was used for this study. The CSF samples were clear and colorless and had normal cell counts. Blood was collected into tubes with ethylenediaminetetraacetic acid (EDTA), and CSF drawn into glass tubes. These were placed immediately on ice. The plasma was separated and EDTA was added to an aliquot of the CSF and all samples were kept at −20°C.

Methods

Plasma and CSF catecholamines were measured by the fluorimetric method of Renzini et al., as modified by Miura et al. Cerebrospinal fluid NE was measured by the method of Peuler and Johnson in one patient. Plasma NE measured by the Renzini method was identical to that of the radioenzymatic method in this patient. Plasma renin activity (PRA) was measured by the method of Haber et al., at pH 6.8 with 8-hydroxy-quinoline, and dopamine-beta-hydroxylase (DBH) according to Nagatsu and Udenfriend. Unless otherwise stated, the data are presented as means ± sd. Statistical probability of differences was calculated by Student's t test and regression lines and correlation coefficients by the method of least squares. Differences and correlation coefficients were considered statistically significant at p < 0.05.

### Table 1. Age, Sex, CSF Norepinephrine and Neurological Disorders in 26 Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient No.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>CSF NE (ng/l)</th>
<th>Neurological disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive</td>
<td>1</td>
<td>32</td>
<td>M</td>
<td>154</td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>28</td>
<td>M</td>
<td>156</td>
<td>Idiopathic Bell's palsy</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>25</td>
<td>F</td>
<td>147</td>
<td>Pseudotumor cerebri</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>40</td>
<td>M</td>
<td>173</td>
<td>Amyloidotic disease</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>46</td>
<td>M</td>
<td>255</td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>28</td>
<td>M</td>
<td>246</td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>36</td>
<td>F</td>
<td>42</td>
<td>Headache</td>
</tr>
<tr>
<td>Normotensive</td>
<td>8</td>
<td>54</td>
<td>M</td>
<td>48</td>
<td>Seizures</td>
</tr>
<tr>
<td>with phenytoin</td>
<td>9</td>
<td>33</td>
<td>F</td>
<td>93</td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>36</td>
<td>F</td>
<td>34</td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>21</td>
<td>F</td>
<td>52</td>
<td>Seizures</td>
</tr>
<tr>
<td>Primary hypertensive</td>
<td>12</td>
<td>33</td>
<td>F</td>
<td>338</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>62</td>
<td>F</td>
<td>203</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>40</td>
<td>M</td>
<td>340</td>
<td>Paralysis, arm and leg</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>50</td>
<td>M</td>
<td>223</td>
<td>Syncope, dizziness</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>31</td>
<td>F</td>
<td>351</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>23</td>
<td>M</td>
<td>317</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>42</td>
<td>F</td>
<td>317</td>
<td>Seizures</td>
</tr>
<tr>
<td>Secondary hypertensive</td>
<td>19</td>
<td>31</td>
<td>F</td>
<td>66</td>
<td>Headache</td>
</tr>
<tr>
<td>Pheo</td>
<td>20</td>
<td>34</td>
<td>F</td>
<td>nil</td>
<td>Headache</td>
</tr>
<tr>
<td>RVH</td>
<td>21</td>
<td>23</td>
<td>M</td>
<td>202</td>
<td>Dizziness, headache</td>
</tr>
<tr>
<td>GBS</td>
<td>22</td>
<td>24</td>
<td>M</td>
<td>177</td>
<td>Guillain-Barré-Syndrome</td>
</tr>
</tbody>
</table>

Abbreviations: NE = norepinephrine, Pheo = pheochromocytoma; RVH = renovascular hypertension; GBS = Guillain-Barré-Syndrome; CSF = cerebrospinal fluid;
Results

Blood Pressure, Catecholamines and Age

The mean arterial blood pressure of the hypertensive patients was greater than that of normotensive subjects, whether treated or not with phenytoin ($p < 0.01$) (table 2). The means of the standing mm Hg blood pressure were $138 \pm 12$ systolic and $96 \pm 10$ diastolic in hypertensives and $113 \pm 11$ and $82 \pm 6$, respectively, in normotensives. The supine pulse rates were slightly higher in the phenytoin-treated subjects ($94 \pm 12$) than in the other normotensive ($74 \pm 7$, $p < 0.05$) or hypertensive patients ($73 \pm 11$, $p < 0.05$). The supine blood pressure at the time of the study was not different from measurements taken on admission to the hospital. The means of the CSF NE and supine plasma NE of the hypertensive patients were $80\%$ and $44\%$ greater than respective values of the normotensive subjects ($p < 0.001$, and $p < 0.05$, respectively). The CSF NE of the normotensive and primary hypertensive patients was related to their supine plasma NE concentration ($p < 0.05$) (fig. 1). The mean CSF NE of normotensives taking phenytoin was $66\%$ less than the mean of the other normotensive subjects ($p < 0.001$). Supine plasma NE of the normotensive patients taking phenytoin was greater than in the other two groups. The difference from the normotensive patients not taking phenytoin was significant ($p < 0.05$). Standing plasma catecholamines were not different among the three groups.

The CSF NE of all normotensive and primary hypertensive patients was related to the systolic ($r = 0.55$, $p < 0.05$) and diastolic blood pressure ($r = 0.71$, $p < 0.001$) (fig. 2) at the time of the study and at the time of admission: $r = 0.47$, $p < 0.05$ and $r = 0.59$, $p < 0.01$, respectively.

In 13 of 17 subjects CSF epinephrine was not detectable. The CSF NE of the hypertensive patients was correlated inversely with age ($r = -0.83$, $p < 0.01$) (fig. 3). Plasma NE was correlated directly with age of the normotensive subjects not taking phenytoin ($r = 0.89$, $p < 0.01$), but was not correlated significantly with systolic or diastolic blood pressures; $r = 0.38$, and $0.47$, respectively ($p > 0.05$) or with...
natural log PRA of the combined untreated nor-motensive and hypertensive patients. Plasma epinephrine concentration was similar in each group and not related to age or blood pressure.

CSF and Plasma DBH and Plasma Renin Activity

The mean CSF DBH was less than 2% of the plasma values (table 2). There were no differences in DBH found among the three groups. Mean plasma DBH of the hypertensive patients was 40% greater than normotensive subjects and increased with standing; however, the differences were not significant.

Mean plasma renin activity of this hypertensive group was greater than in normotensive subjects, but the difference was not significant. We found CSF NE was directly related to natural log PRA of the hypertensive patients \( r = 0.74, p < 0.05 \).

Patients with Secondary Hypertension

The individual CSF NE of the patients with secondary hypertension was less than any of the patients with primary hypertension (table 2). The plasma NE concentrations in patients with pheochromocytoma were 10 and 20 times greater than the mean of the normotensive patients.

Discussion

We found increased concentrations of NE in the CSF of younger patients with primary hypertension. The source and cause of the elevated CSF NE concentrations in the hypertensive patients have not been characterized. Norepinephrine is an important neurotransmitter of the central nervous system where it is inactivated by reuptake and metabolism.\(^{15,16}\) Norepinephrine is present throughout the brain and the grey matter of the spinal cord, but is particularly concentrated in areas involved in blood pressure regulation, such as the brain stem and hypothalamus. Also, the regions richest in NE are located close to the CSF.\(^{17}\) Release of NE from the brain has a marked effect on the NE levels in the CSF, since the NE concentration in several brain areas is 1000 times greater than that in CSF. A blood-brain barrier for catecholamines has been demonstrated in this study and by others.\(^{18}\) Therefore, it is unlikely that NE in CSF is derived from blood NE. Thus, NE levels in CSF represent the amount of NE released into the CSF minus the amount eliminated by reuptake and/or metabolic conversion.

The raised CSF NE in our hypertensive patients may be related to increased brain NE release, reflecting enhanced central neurogenic tone. Ziegler et al.\(^{19}\) have found circadian variation of NE in man and monkeys. They related peak levels of CSF NE in the animals to an increased rate of release of NE from nerve endings during the most active part of the day. Increased CSF NE does not, of itself, indicate that overactivity of the central sympathetic nervous system causes primary hypertension. Catecholaminergic neurons in the brain stem\(^{20}\) and hypothalamus\(^{21}\) are important in regulating blood pressure in animal models with hypertension and NE turnover was decreased in parts of the hypothalamus of the spontaneously hypertensive rat.\(^{22}\) Increased CSF NE could be indicative of overactivity of inhibitory blood pressure controlling systems, in response to increased blood pressure. However, our findings of normal or low CSF NE in patients with secondary hypertension argue against this possibility. Alternatively, a stimulated NE pathway could cause both the increased CSF NE and blood pressure.

Diverse factors might affect sympathetic nerve function and alter CSF NE in our human subjects. Differences between the groups due to concentration

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### Table 2. Age, Systolic and Diastolic Blood Pressure (BP), Cerebrospinal Fluid (CSF) and Plasma Catecholamines (CA), Plasma Dopamine-Beta-Hydroxylase (DBH) and Plasma Renin Activity (PRA) in the Different Groups (Means ± sd)

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yrs)</th>
<th>Supine BP (mm Hg)</th>
<th>CSF CA (ng/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
</tr>
<tr>
<td>Normotensive (n = 7)</td>
<td>36 ± 10</td>
<td>120 ± 10</td>
<td>74 ± 9</td>
</tr>
<tr>
<td>Normotensive with phenytoin</td>
<td>36 ± 14</td>
<td>117 ± 14</td>
<td>71 ± 10</td>
</tr>
<tr>
<td>Primary hypertensive (n = 7)</td>
<td>40 ± 13</td>
<td>144 ± 10‡</td>
<td>92 ± 4*</td>
</tr>
<tr>
<td>Secondary hypertensive (n = 4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pheo</td>
<td>34</td>
<td>136</td>
<td>82</td>
</tr>
<tr>
<td>Pheo</td>
<td>32</td>
<td>165</td>
<td>110</td>
</tr>
<tr>
<td>RVH</td>
<td>23</td>
<td>180</td>
<td>129</td>
</tr>
<tr>
<td>GBS</td>
<td>24</td>
<td>128</td>
<td>82</td>
</tr>
</tbody>
</table>

* = \( p < 0.001 \).
† = \( p < 0.005 \).
‡ = \( p < 0.01 \).

Abbreviations: NE = norepinephrine; E = epinephrine, ND = non-detectable, DBH unit = nmole octopamine formed ml\(^{-1}\) min\(^{-1}\); Pheo = pheochromocytoma; RVH = renovascular hypertension; GBS = Guillain-Barre-Syndrome.
increased plasma NE in patients treated with phenytoin has not been clarified. However, phenytoin is known to reduce calcium concentration and inhibit beta-hydroxylase and noradrenaline amounts in essential hypertension. Circ Res 38: 109, 1976


There appears to be an excellent correlation of plasma NE with CSF NE and since there is a blood-brain barrier for norepinephrine, it is likely that plasma NE reflects a major aspect of central NE tone. Furthermore, we found correlations of CSF NE with systolic and diastolic blood pressures, which suggest that an increased central release of NE is associated with an augmented peripheral sympathetic tone and elevated blood pressure. Although the findings in this small group of subjects cannot be extrapolated to hypertensive patients in general, they suggest that central NE tone is enhanced in some hypertensive patients, especially in younger patients with increased plasma NE and renin activity.

Acknowledgments
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